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Physical activity is associated with lower arterial stiffness in older adults: results of the SAPALDIA 3 Cohort Study

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Abstract: Associations of physical activity (PA) intensity with arterial stiffness in older adults at the population level are insufficiently studied. We examined cross-sectional associations of self-reported PA intensities with arterial stiffness in elderly Caucasians of the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults. Mixed central and peripheral arterial stiffness was measured oscillometrically by the cardio-ankle vascular index (CAVI) and brachial-ankle pulse wave velocity (baPWV). The self-reported International Physical Activity Questionnaire long version was administered to classify each subject's PA level. We used univariable and multivariable mixed linear and logistic regression models for analyses in 1908 persons aged 50 years and older. After adjustment for several confounders moderate, vigorous and total PA were inversely associated with CAVI (p = 0.02-0.03). BaPWV showed negative and marginally significant associations with vigorous and moderate PA (each p = 0.06), but not with total PA (p = 0.28). Increased arterial stiffness (CAVI 9, upper tertile) was inversely and significantly associated with vigorous PA [odds ratio (OR) 0.65, 95 % confidence interval (CI) 0.48-0.88], and marginally significantly with total PA (OR 0.76, 95 % CI 0.57-1.02) and moderate PA (OR 0.75, 95 % CI 0.56-1.01). The odds ratio for baPWV 14.4 was 0.67 (95 % CI 0.48-0.93) across the vigorous PA levels, and was non-significant across the total (OR 0.91, 95 % CI 0.66-1.23) and moderate PA levels (OR 0.94, 95 % CI 0.69-1.28). In this general Caucasian population of older adults higher levels especially of vigorous PA were associated with lower arterial stiffness. These data support the importance of PA for improving cardiovascular health in elderly people.

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Title: **Physical Activity is Associated With Lower Arterial Stiffness in Older Adults: Results of the SAPALDIA 3 Cohort Study**

Short title: **Physical activity and arterial stiffness**

Running head: **Physical activity and arterial stiffness**

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Abstract

Associations of physical activity (PA) intensity with arterial stiffness in older adults at the population level are insufficiently studied. We examined cross-sectional associations of self-reported PA intensities with arterial stiffness in elderly Caucasians of the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA). Mixed central and peripheral arterial stiffness was measured oscillometrically by the cardio-ankle vascular index (CAVI) and brachial-ankle pulse wave velocity (baPWV). The self-reported International Physical Activity Questionnaire (IPAQ) long version was administered to classify each subject's PA level. We used univariable and multivariable mixed linear and logistic regression models for analyses in 1908 persons aged 50 years and older. After adjustment for several confounders moderate, vigorous and total PA were inversely associated with CAVI ($p = 0.02$-0.03). BaPWV showed negative and marginally significant associations with vigorous and moderate PA (each $p = 0.06$), but not with total PA ($p = 0.28$). Increased arterial stiffness (CAVI ≥ 9, upper tertile) was inversely and significantly associated with vigorous PA (Odds Ratio (OR) = 0.65, 95% Confidence Interval (CI): 0.48-0.88), and marginally significantly with total PA (OR = 0.76, 95% CI: 0.57-1.02) and moderate PA (OR = 0.75, 95% CI: 0.56-1.01). The odds ratio for baPWV ≥ 14.4 was 0.67 (95% CI: 0.48-0.93) across the vigorous PA levels, and was non-significant across the total (OR = 0.91, 95% CI: 0.66-1.23) and moderate PA levels (OR = 0.94, 95% CI: 0.69-1.28). In this general Caucasian population of older adults higher levels especially of vigorous PA were associated with lower arterial stiffness. These data support the importance of PA for improving cardiovascular health in elderly people.

Keywords: arterial stiffness, cardiovascular disease prevention, epidemiology, physical exercise, prevention

Background

Physical inactivity is regarded as one of the main risk factors for both non-communicable diseases in general and cardiovascular diseases in particular [1]. 6% of the burden of disease from coronary heart disease and 9% of premature deaths worldwide in 2008 are attributable to physical inactivity [2]. Adherence to physical activity (PA) guidelines is suggested to reduce the mortality rate by 25% [3] and an increase of PA by 10% or 25% could prevent more than 533’000 or 1.3 million deaths, respectively, per year worldwide [2]. A physically active lifestyle is linked with decreased risk of cardiovascular diseases and events at all ages through improvements in arterial stiffness reflecting arterial remodeling [4–6]. Arterial stiffness is a reversible, non-invasive structural biomarker of potentially grave cardiovascular modifications and is independently associated with cardiovascular disease and events [7,8]. Stiffening of the arteries is closely linked with ageing related elastin degeneration and collagen proliferation reflecting vascular ageing [9].

The current European Guidelines on cardiovascular disease prevention in clinical practice of the European Society of Cardiology [10] and physical activity guidelines [11] recommend a minimum of 150 minutes per week of at least moderate intensity for adults to beneficially impact on the population health and cardiovascular mortality. However, in larger samples associations between PA intensities and arterial stiffness have so far mainly been analyzed regarding central arterial stiffness in adolescents and middle-aged persons [12–15]. In two population based studies of older adults walking speed was inversely associated with central arterial stiffness [16,17]. Besides, there are only two medium sized cross-sectional studies showing that PAs of different intensities are associated with lower central arterial stiffness in older adults [18,19].

The cardio-ankle vascular index (CAVI) and brachial-ankle pulse wave velocity (baPWV) are mixed measures of central and peripheral arterial stiffness that have mainly been studied in Asian populations so far [20,21]. There are no data on the population level in older adults of the association between different intensities of PA and arterial stiffness measured by CAVI and baPWV. Therefore, we examined associations of self-reported PA intensities with these arterial stiffness indices in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA).

Methods

Study design and participants

SAPALDIA 3 is the second follow-up assessment of an ongoing multi-center cohort study including eight distinct rural and urban areas which represent the environmental and demographic diversity of Switzerland (Aarau, Basel, Davos, Geneva, Lugano, Montana, Payerne, Wald) [22,23]. SAPALDIA was initiated in 1991 to investigate the association of air pollution and lung diseases among randomly selected adults (18 to 60 years, N = 9651). SAPALDIA 3 additionally focused on cardiovascular health assessment and arterial stiffness was measured in 3068 subjects of the cohort aged at least 50 years. The respective Swiss cantonal ethical committees have granted ethical approval and participants gave written informed consent.

Arterial stiffness measurement

Mixed central and peripheral arterial stiffness was measured oscillometrically and simultaneously by CAVI and baPWV using a non-invasive VaSera VS-1500N vascular screening system (Fukuda Denshi, Tokyo, Japan). All measurements were taken in supine position after ten minutes of rest in a quiet room with constant temperature. Blood cuffs were placed at each upper arm and above each ankle. ECG electrodes at each wrist and a phonocardiogram on the sternal border in the second intercostal space were applied to detect the initial notch of the pulse waves at the heart and the ankle on average over six heart cycles. The time delay of the pulse wave from the heart to the ankle was determined by a foot-to-foot-method. Vascular length between the heart valve and the ankle artery was estimated by the VSS-10 software (Fukuda Denshi) using a height based formula [24]. The PWV is calculated by dividing the arterial length by the time delay of the pulse wave. CAVI is then automatically derived from Bramwell-Hill´s equation and the stiffness parameter ß with an inclusion of the PWV [25]. Therefore, CAVI is less dependent on blood pressure at the time of measurement than aortic PWV[26] and baPWV [27]. The average of two consecutive measurements at 3-5 minute intervals and of both body sides was taken for analyses. The CAVI and baPWV reproducibility was previously shown to be high in this Caucasian cohort [28]. CAVI reflects arterial stiffness of the aorta and the iliac, femoral and tibial arteries [25] and baPWV between the brachial and tibial arteries [29]. Since both of these indices cover different segments of the arterial tree, they reflect a combination of central and peripheral arterial stiffness [20,21].

Physical activity assessment

The self-reported International Physical Activity Questionnaire (IPAQ) long version was administered to classify the PA level in 3072 individuals [30]. The IPAQ long form asks for the frequency and duration of moderate and vigorous PA in different domains performed during the last seven days (leisure time PA, domestic and gardening (yard) activities, work-related PA, transport-related PA) [31]. Moderate and vigorous intensities were associated with harder and much harder breathing, respectively. Minutes per week of moderate PA (including walking), vigorous PA and total PA as a sum of minutes per week of moderate and vigorous PA were calculated following the IPAQ guidelines [31]. They were weighted by their energy cost as metabolic equivalents (MET) with one MET equating to around one kcal/kg/hour, which approximately corresponds to sitting quietly. This leads to a MET-minutes per week score reflecting total energy expenditure [32]. Total PA is therefore a combined measure of amount and intensity of PA in terms of MET-minutes per week of moderate and vigorous PA. We calculated levels ("low", "medium" and "high") of each category of PA (moderate, vigorous and total PA). Levels of moderate and total PA were calculated by tertile classes. Vigorous PA was not categorized in tertiles due to the clustering of answers (56.8% of subjects reported no vigorous PA and 6.2% reported 960 MET-min/week of vigorous PA). All subjects without vigorous PA were assigned to the lowest level of vigorous PA (N=1084). Since 118 subjects reported on exactly 960 MET-min/week of vigorous PA corresponding to the threshold between the medium and high level of vigorous PA, these subjects were all assigned to the medium level to achieve the best possible balance of group sizes. Thus, the chosen categorization of vigorous PA is the best approximation to a categorization by tertiles as for moderate and total PA.

Statistical analyses

If not stated otherwise, data are expressed as median (25^{th} and 75^{th} percentile). Comparisons of the variables of interest by PA levels were performed by using t test, nonparametric median test (Kruskal Wallis test) or χ^2 test, as appropriate and age associations by linear regression. CAVI and baPWV were analyzed as continuous outcomes and when stated in dichotomized form, with a threshold for increased arterial stiffness of 9 for CAVI (comparing the highest to the lower two tertiles) and of 14.4 m/s for baPWV (comparing the highest to the lower two tertiles), respectively. We used univariable (Model 1) and multivariable mixed linear and logistic regression models for analyses including a random area effect to account for the multi-center study setting. In Model 2, the association of arterial stiffness with PA was adjusted for age and sex and in Model 3 additionally for body mass index, smoking status defined as packyears up to SAPALDIA 3, educational status, mean arterial pressure, heart rate, and medication. Medication intake was categorized in two classes: 0, no cardiovascular or metabolic disease related medication; 1, medication for kidney disease, diabetes, hyperlipidemia, hypertension, stroke, myocardial infarction, heart failure, angina and arrhythmia. We a priori defined and investigated several potentially important interactions and included the interaction terms age-sex and sex-mean arterial pressure in the final Model 4 based on the inclusion criteria $p = 0.1$. We used backward selection of variables using the Akaike Information Criterion (AIC) and tested non-linear terms using residual-versus-predicted-plots to derive the best fitting model. All statistical analyses were performed using the statistical software STATA (StataCorp LP, Release 12, Texas, USA) with $p = 0.05$ as significance level.

Results

Subject Characteristics

In 1908 out of 3068 individuals data of both arterial stiffness and IPAQ were available. The analytic sample was on average significantly older (63.3 vs 58 years, $p < 0.001$) and had significantly lower baPWV (13.8 vs 14.1 m/s, $p < 0.001$), body mass index (26.1 vs 26.5 kg/m2, $p < 0.05$), total PA (5279 vs 5810 MET-min/week, $p < 0.05$), vigorous PA (1023 vs 1454 MET-min/week, $p < 0.001$), mean arterial pressure (99.3 vs 100.3 mmHg, $p < 0.05$) and heart rate (61.9 vs 63.1 bpm, $p < 0.05$) compared to the whole arterial stiffness and IPAQ sample of SAPALDIA 3. CAVI, moderate PA and the number of smoking packyears were not significantly different. The main characteristics by vigorous PA levels are listed in Table 1.

Associations of Age and Sex With Physical Activity and Arterial Stiffness

A significant sex difference with respect to PA was present only in vigorous PA with higher values in males ($p < 0.001$) (Supplemental Table S1). There was a significant age associated decline in total PA for females ($p < 0.01$ oldest to youngest age category), but not for males (p

= 0.71) (Supplemental Table S2). Vigorous PA decreased significantly in both sexes with increasing age category ($p < 0.001$ oldest to youngest age category). Moderate PA increased in both sexes from the age of 50-59 years to 60-69 years, significantly only in males ($p < 0.01$; females $p = 0.09$), and decreased in older participants with higher amounts of moderate PA compared to age 50-59 years significant only in males ($p = 0.03$), but not in females ($p = 0.53$). CAVI and baPWV increased significantly with age in both sexes (every $p < 0.001$); CAVI on average by 0.9 per decade and baPWV by 1.8 m/s, respectively (Supplemental Fig. S1). Statistically significant gender differences were observed for CAVI in the age groups 60-69 ($p < 0.001$) and 70-81 ($p < 0.01$) and for baPWV in the age groups 50-59 ($p = 0.01$) and 60-69 ($p < 0.01$) , with lower values among women (Supplemental Fig. S1).

Association of Physical Activity With Arterial Stiffness

In the univariable analyses the means of CAVI and baPWV both decreased across levels of moderate, vigorous and total PA, however significantly only for vigorous PA (every $p < 0.001$), where more than a third of the participants did not report on any vigorous PA Table 3 and 4 show the regression results for CAVI and baPWV as a function of PA for each of the four models. In the multivariable analyses of CAVI there was a significant inverse association of CAVI with PA after adjustment in Model 2 for total and vigorous PA comparing the high with the low PA level (each $p = 0.04$) and for moderate PA comparing the medium with the low PA level ($p = 0.03$), but not between high and low PA ($p = 0.09$).This inverse association was strengthened upon further adjustment in Model 3 with significant associations between the high and low PA level for total ($p = 0.03$) and vigorous PA ($p = 0.02$) and marginally significant for moderate PA comparing medium and low PA ($p = 0.05$), but not high and low PA ($p = 0.10$). Inclusion of the interaction terms age-sex and sex-mean arterial pressure in Model 4 further strengthened the associations of CAVI with the respective PA levels ($p = 0.02$-0.03). BaPWV showed negative and marginally significant associations with vigorous

PA comparing the high with the low level and with moderate PA comparing the medium with the low level (each $p = 0.06$), but not significantly with total PA after adjustment in Model 3 and 4.

There was a significant positive age-sex (each $p = 0.03$) and marginally significant positive sex-mean arterial pressure interaction (each $p = 0.05$) in the models estimating the association between CAVI and PA. With increasing mean arterial pressure, the sex difference in CAVI increased, with higher values in males for moderate, vigorous and total PA (exemplarily for total PA in Supplemental Fig. S2). The interaction terms were not statistically significant in the baPWV models.

The fully adjusted (Model 4) CAVI means decreased significantly from 8.67 to 8.56 from the high to the low total PA level, similarly from 8.64 to 8.53 for vigorous PA and from 8.67 for the low moderate PA level to 8.57 for the medium moderate PA level (Fig 1). The fully adjusted baPWV means decreased non-significantly from 13.78 to 13.65 m/s across total PA levels (from low to medium), from 13.77 to 13.60 m/s for vigorous PA (from low to high) and from 13.80 to 13.63 m/s for moderate PA (from low to medium).

Odds Ratios

The marginal probability of CAVI ≥ 9 decreased from 0.37 to 0.31 ($p < 0.01$) significantly across vigorous PA levels with an odds ratio (OR) of 0.65 (95% Confidence Interval (CI): 0.48-0.88) for the highest level compared to the lowest, and marginally significant from 0.37 to 0.33 across total PA levels ($p = 0.07$, OR 0.76, 95% CI: 0.57-1.02), and from 0.38 to 0.34 across moderate PA levels ($p = 0.06$, OR 0.75, 95% CI: 0.56-1.01). These results are derived from mixed logistic regression analyses with the same adjustment as in Model 4 (Table 2 and Supplemental Fig S3). Similarly, the marginal probability of baPWV ≥ 14.4 decreased significantly from 0.33 to 0.28 for vigorous PA levels ($p = 0.02$, OR 0.67, 95% CI: 0.48-

0.93), but non-significantly across the total (from 0.33 to 0.32, p = 0.53, OR 0.91, 95% CI: 0.66-1.23) and moderate PA levels (from 0.33 to 0.32, p = 0.69, OR 0.94, 95% CI: 0.69-1.28).

Discussion

The results of this cross-sectional study in a very well characterized cohort of elderly Caucasian subjects from the general population suggest that higher levels of self-reported PA are associated with lower arterial stiffness, even after adjustment for several potential confounders. Especially vigorous PA was linked with lower arterial stiffness in this ageing population. These data support the importance of PA for improving cardiovascular health in elderly people and suggest that vigorous PA promotion in this age group may prevent against increased arterial stiffness resulting from atherosclerotic processes.

Our results are in agreement with previous cross-sectional studies which suggest that higher levels of PA may have a protective effect on the vascular system [16,17]. Thereby, it has to be kept in mind, that the effect of PA on arterial stiffness varies across the arterial tree [15,33]. In a comparable cohort of older adults of the Whitehall II study higher arterial stiffness measured as carotid-femoral PWV was strongly associated with reduced walking speed and self-reported physical functioning [16]. Similarly, lower walking speed was linked with increased carotid-femoral PWV in a general population aged 70-79 years of the Health ABC Study, however, this association was dependent on the presence of hypertension and other vascular risk factors [17]. Aoyagi et al. examined the association of habitual PA (>3 metabolic equivalents) measured by step counts and arterial stiffness in 198 Japanese people aged 65-84 years [33]. They reported on a beneficial effect of PA on the stiffening of central arteries, but not on the peripheral vasculature. Controversial results can be found regarding the intensity-dependence of this PA effect. In a medium sized longitudinal study particularly PA at higher intensity was favorable regarding central and peripheral arterial stiffness in younger persons [14,15]. In the only study analyzing baPWV and PA intensities an increase in moderate-to-vigorous PA, but not light intensity PA, was linked with a decrease of baPWV in 274 overweight and obese young adults longitudinally within one year [20]. In 103 postmenopausal women moderate and vigorous PA was inversely associated with central arterial stiffness [19]. Yet, also long-term maintenance of low intensity PA was associated with lower central arterial stiffness in older adults [18].

Intervention studies with rather small sample sizes have demonstrated that arterial stiffness may be modifiable by exercise training in older adults [34–36]. A one year vigorous endurance exercise program improved arterial stiffness indices in twelve persons aged on average 70.3 years, who were sedentary before [34]. However, a short-term twelve week moderate intensity PA program did not change arterial stiffness in 113 persons aged 50-80 [37]. Five recent systematic reviews of intervention studies show conflicting results concerning the effects of exercise interventions on arterial stiffness. Two of them found a significant positive effect of aerobic exercise on arterial stiffness especially at higher intensity [35,36], however neither in pre- and hypertensive [38] nor in middle-aged and older obese persons [39]. The results regarding resistance training are controversial ranging from negative effects [40] to beneficial effects depending on the intensity, muscle groups involved and the movement execution [35,36]. The discrepancies in these results may be due to whether or not non-randomized controlled trials have been included in the reviews, small sample sizes for subgroup analyses, different arterial stiffness measures, and varying statistical analyses. Thus, intervention study results show that there are beneficial effects of exercise training on arterial stiffness depending on the intensity and modality [34–37]. Our results show an association in line with these intervention study effects in terms of a beneficial relationship between higher amounts of regularly performed PA, especially at higher intensity, on arterial stiffness in older adults at the population level.

CAVI and baPWV are valid vascular biomarkers for non-invasive arterial stiffness assessment and are associated with cardiovascular disease risk and outcomes [41–44]. Both CAVI and baPWV have shown good correlations with central arterial stiffness [29,45]. In a systematic review of clinical studies, a 1 m/s reduction in baPWV was associated with an increase in total cardiovascular events, cardiovascular mortality, and all-cause mortality by 12%, 13%, and 6%, respectively [43].CAVI is methodologically based on the baPWV measurement with improvements regarding the correlation with blood pressure [25]. Since CAVI is mathematically derived from the stiffness parameter β and a modified Bramwell-Hill equation, CAVI could be shown to be less dependent on the blood pressure at the time of measurement compared to baPWV [27]. CAVI includes stiffness of the aorta, femoral artery and tibial artery [25], whereas baPWV reflects the PWV to the upper arm and foot ignoring the influence of PWV to the arm as a possible modifier of the overall stiffness without precise definition of the distance from the heart to the upper arm [46]. These differences between CAVI and baPWV might explain that both indices do not show exactly the same results concerning their association with PA. However, they point to consistent conclusions towards lower arterial stiffness with higher PA.

CAVI and baPWV were on average 0.10 and 0.16 m/s, respectively, lower in persons of the high PA level compared to the low PA level across moderate, vigorous and total PA in the fully adjusted Model 4. Thereby, it has to be kept in mind that moderate and total PA levels have been generated according to tertiles of MET-min/week, while this was not possible for vigorous PA where more than a third of subjects (N=1084) did not report on any vigorous. In this general population aged 50 to 81 years, CAVI increased significantly on average by 0.87 per decade and baPWV by 1.84 m/s (see Supplemental Fig. S3). Therefore, higher levels of PA were associated with a favorable decrease of CAVI corresponding to around 1.1 years and for baPWV to 0.9 years of age related decrease in arterial stiffness independent of the main confounding factors. This strengthens the evidence that PA can be implemented in cardiovascular health guidelines to counteract the vascular aging process and prevent early vascular aging as suggested by Nilsson et al. [9].Nevertheless, due to the cross-sectional design of this study causality and reverse causality concerning PA and arterial stiffness cannot be answered. Up-to-date there are no studies on sedentary behavior and systemic arterial stiffness, however sitting time has been shown to be related to higher wave reflections [47], augmentation index [48] and carotid arterial stiffness [49].

Presently, there are no comparable IPAQ data for a Swiss population based cohort. According to the Eurobarometer 64.3 our study sample of the Swiss general population of older adults would rank as one of the most active European nations (median total PA 3971 MET-minutes/week) [50]. This is in line with reports that 73% of Swiss adults meet the current PA guidelines according to the recent Swiss health survey [51] and is consistent with the 2014 Swiss report on sports activity, in which Switzerland ranks 2nd behind Sweden in a European comparison [52,53]. However, only 43% of our ageing population reported on vigorous PA. This part of the population showed a beneficial inverse association of vigorous PA with arterial stiffness compared to subjects without vigorous PA. This result indicates that population based PA interventions and guidelines for older adults should incorporate and promote vigorous PA to improve cardiovascular health.

Self-reported medication is commonly used for assessing disease in epidemiological studies and is related to diagnosed disease as shown for diabetes [54]. Assessment of disease by self-report of medication may be prone to information bias due to non-reporting leading to misclassification. However, it can be assumed that this would be nondifferential misclassification without affecting the estimates in this cohort study. Besides, medical treatment is commonly based on clear disease indications and it has been shown, that self-reported medical history is accurately related to cardiovascular and metabolic disease [56,57].

Furthermore, patients' self-reported cardiovascular and diabetic medication use has been found to be reliable [58].

Study Limitations

This is a cross-sectional study, which does not enable inferring a causal association between PA and arterial stiffness in these adults aged at least 50 years. Reporting bias might have affected the self-reported PA assessment. However, the IPAQ has been developed and validated by Craig et al. as a cross-national monitoring tool of PA and physical inactivity for adults aged 15-69 years and represents a feasible, reliable and valid measurement instrument of PA [30]. While the IPAQ is prone to over-estimating PA especially in adults aged ≥65 years [59], this is less the case for vigorous PAs such as structured sports or exercise activities [60], which showed the strongest association with arterial stiffness in our study. Due to logistic and financial reasons, objective PA measurements could not be implemented in the current study.

Conclusions

In summary, PA of higher intensity was independently associated with lower mixed central and peripheral arterial stiffness in this cross-sectional analysis of a cohort of older adults. The probability of having increased arterial stiffness was lower in more physically active persons. Regular vigorous PA may counteract vascular aging and, thus, reduce the population risk of cardiovascular disease and events. It is highly recommended to further strengthen the significance of vigorous PA in cardiovascular health guidelines in these age groups.

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Conflict of Interest The authors declare no conflict of interest.

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Figure legends

Fig. 1 Fully adjusted (Model 4) means of cardio-ankle-vascular-index (CAVI) and brachial-ankle pulse wave velocity (baPWV) across total, vigorous and moderate physical activity (PA) levels. * $p < 0.05$ compared to low PA level.

Supplemental figure legends

Fig. S1 Box plots of cardio-ankle-vascular-index (CAVI) and brachial-ankle pulse wave velocity (baPWV) by sex and age. Box represents 25th percentile (lower edge), median (middle bar) and 75th percentile (upper edge). Whiskers show the extent of the rest of the data; points indicate outliers.

Fig. S2 Fully adjusted (Model 4) means of cardio-ankle-vascular-index (CAVI) over mean arterial pressure by sex and total physical activity (PA) levels (low, medium, high).

Fig. S3 Marginal probability of cardio-ankle vascular index (CAVI) >=9 and brachial-ankle pulse wave velocity (baPWV) >=14.4 m/s across total, vigorous and moderate physical activity (PA) levels. * $p < 0.05$ compared to low PA level.

Figure 1
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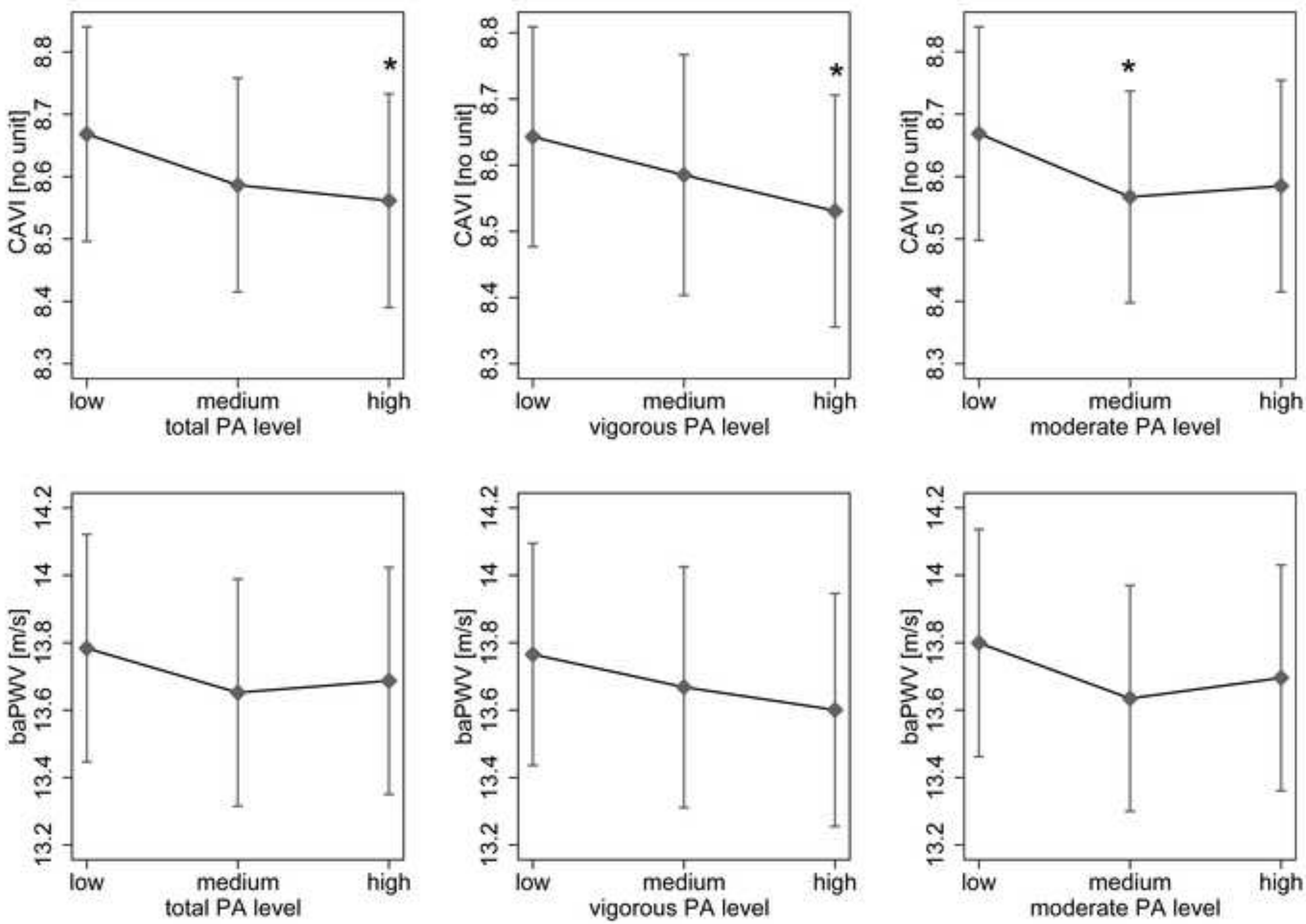

tables 1-4
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Table 1. Study population main characteristics across vigorous physical activity (PA) levels (N=1898).

		Vigorous PA level			
	Units	**Low (N=1084)**	**Medium (N=326)**	**High (N=488)**	**P-value**
Age	years	65.0 (59.0; 70.9)	61.7 (55.8; 66.4)	60.9 (54.7; 66.3)	<0.001
baPWV	m/s	13.07 (12.27; 15.42)	13.00 (11.48; 14.60)	13.00 (11.48; 14.60)	<0.001
CAVI	no unit	8.72 (7.93; 9;47)	8.34 (7.64; 9.20)	8.40 (7.69; 9.05)	<0.001
Mean arterial pressure	mmHg	99 (92; 107)	98 (90; 105)	99 (92; 107)	0.37
Heart rate	bpm	62 (56; 69)	59 (54; 64)	60 (54; 65)	<0.001
Body mass index	kg/m2	26.0 (23.3; 29.1)	25.3 (22.6; 27.5)	25.4 (23.0; 28.3)	0.01
Smoking	packyears	0.4 (0; 20.0)	0 (0; 14.5)	2.0 (0; 20.0)	0.02
Moderate PA	MET-min/week	2832 (1356; 5292)	2753 (1449; 5202)	4821 (2588; 8148)	<0.001
Vigorous PA	MET-min/week	0 (0; 0)	680 (480; 960)	2880 (1860; 4580)	<0.001
Total PA	MET-min/week	2832 (1356; 5292)	3455 (2130; 6036)	8236 (5384; 11909)	<0.001
Medication		N (%)	N (%)	N (%)	
0		647 (34.1)	230 (12.1)	337 (17.8)	<0.001
1		437 (23.0)	96 (5.1)	151 (8.1)	
Medication for		N (%)	N (%)	N (%)	
Kidney disease		3 (0.2)	3 (0.2)	0 (0)	
Diabetes		2 (0.1)	6 (0.3)	14 (0.7)	
Hyperlipidemia		190 (10.0)	42 (2.2)	62 (3.3)	
Hypertension		308 (16.2)	70 (3.7)	103 (5.4)	
Stroke		17 (0.9)	4 (0.2)	5 (0.3)	
Myocardial infarction		20 (1.1)	6 (0.3)	8 (0.4)	
Heart failure		8 (0.4)	2 (0.1)	4 (0.2)	
Angina pectoris		15 (0.8)	1 (0.1)	9 (0.5)	
Arrhythmia		40 (2.1)	8 (0.4)	10 (0.5)	
Education		N (%)	N (%)	N (%)	
Low		64 (3.4)	10 (0.5)	18 (0.9)	
Middle		700 (36.9)	213 (11.2)	328 (17.3)	0.15
High		320 (16.9)	103 (5.4)	142 (7.5)	

BaPWV, brachial-ankle pulse wave velocity; CAVI, cardio-ankle vascular index; Education low, primary school; middle, secondary school, middle school or apprenticeship; high, Technical College or University; Medication 0, no cardiovascular or metabolic disease related medication; 1, medication for kidney disease, diabetes, hyperlipidemia, hypertension, stroke, myocardial infarction, heart failure, angina and arrhythmia; MET, metabolic equivalent; PA, physical activity. Values are median and 25^{th}, 75^{th} percentile or N (%). Percentages and p-values for comparisons across vigorous PA levels. Percentages may not add up to 100% due to rounding.

Table 2. Odds ratios (OR) of cardio-ankle vascular index (CAVI) ≥ 9 and brachial-ankle pulse wave velocity (baPWV) ≥ 14.4 m/s across moderate, vigorous and total physical activity (PA).

		Medium compared to low PA level				**High compared to low PA level**			
Variable	**PA**	**OR**	**95% CI**		***P*-value**	**OR**	**95% CI**		***P*-value**
CAVI	Total	0.87	0.65	1.17	0.36	0.76	0.57	1.02	0.07
	Vigorous	0.91	0.65	1.27	0.60	0.65	0.48	0.88	<0.01
	Moderate	0.75	0.56	1.01	0.06	0.75	0.56	1.01	0.06
baPWV	Total	0.94	0.68	1.29	0.69	0.91	0.66	1.24	0.53
	Vigorous	0.93	0.64	1.34	0.69	0.67	0.48	0.93	0.02
	Moderate	0.89	0.64	1.22	0.46	0.94	0.69	1.28	0.69

Table 3. Adjusted estimates of the association between physical activity (PA) levels and continuous cardio-ankle vascular index (CAVI).

		Model 1					Model 2					Model 3					Model 4					
	Unit	Coef.	95% CI		*P*-value	AIC	Coef.	95% CI		*P*-value	AIC	Coef.	95% CI		*P*-value	AIC	Coef.	95% CI		*P*-value	AIC	Adjusted (Model 4) CAVI mean
Moderate PA level		N=1908				5766	N=1896				4710	N=1890				4620	N=1890				4613	Low: 8.67
medium vs. low	MET-min/week	-0.05	-0.18	0.07	0.39		-0.10	-0.20	-0.01	0.03		-0.09	-0.18	-0.00	0.05		-0.10	-0.19	-0.01	0.03		Medium: 8.57
high vs. low	MET-min/week	-0.03	-0.15	0.10	0.66		-0.08	-0.17	0.01	0.09		-0.077	-0.17	0.01	0.10		-0.08	-0.18	0.01	0.08		High: 8.59
Vigorous PA level		N=1898				5694	N=1886				4686	N=1880				4593	N=1880				4588	Low: 8.64
medium vs. low	MET-min/week	-0.29	-0.43	-0.16	<0.001		-0.06	-0.17	0.04	0.24		-0.05	-0.16	0.05	0.32		-0.06	-0.16	0.04	0.26		Medium: 8.58
high vs. low	MET-min/week	-0.39	-0.50	-0.27	<0.001		-0.10	-0.19	0.01	0.04		-0.11	-0.20	-0.02	0.02		-0.11	-0.20	-0.02	0.02		High: 8.53
Total PA level		N=1908				5763	N=1896				4710	N=1890				4619	N=1890				4613	Low: 8.67
medium vs. low	MET-min/week	-0.06	-0.18	0.06	0.35		-0.08	-0.17	0.02	0.10		-0.08	-0.17	0.01	0.09		-0.08	-0.17	0.01	0.08		Medium: 8.59
high vs. low	MET-min/week	-0.11	-0.24	0.01	0.07		-0.10	-0.19	-0.01	0.04		-0.10	-0.19	-0.01	0.03		-0.10	-0.20	-0.01	0.03		High: 8.56

AIC, Akaike Information Criterion; MET, metabolic equivalent.
Model 1: univariable including a random area effect
Model 2: further adjusted for age, sex, body mass index, education and packyears of smoking
Model 3: further adjusted for mean arterial pressure, heart rate and medication
Model 4: further adjusted for interactions age-sex and sex-mean arterial pressure

Table 4. Adjusted estimates of the association between physical activity (PA) levels and continuous brachial-ankle pulse wave velocity (baPWV).

		Model 1					**Model 2**					**Model 3**					**Model 4**					Adjusted (Model 4) PWV
	Unit	Coef.	95% CI		*P*-value	AIC	Coef.	95% CI		*P*-value	AIC	Coef.	95% CI		*P*-value	AIC	Coef.	95% CI		*P*-value	AIC	mean [m/s]
Moderate PA level		N=1907				8623	N=1895				7722	N=1889				6968	N=1889				6972	Low: 13.80
			-					-	-				-					-				Medium: 13.63
medium vs. low	MET-min/week	-0.21	0.48	0.05	0.11		-0.27	0.48	0.06	0.01		-0.16	0.33	0.01	0.06		-0.16	0.33	0.01	0.06		
			-					-					-					-				High: 13.70
high vs. low	MET-min/week	-0.10	0.36	0.16	0.45		-0.18	0.38	0.03	0.09		-0.10	0.27	0.07	0.24		-0.10	0.27	0.07	0.25		
Vigorous PA level		N=1897				8535	N=1885				7688	N=1879				6937	N=1879				6940	Low: 13.77
			-	-				-					-					-				Medium: 13.67
medium vs. low	MET-min/week	-0.77	1.05	0.48	<0.001		-0.19	0.43	0.04	0.11		-0.10	0.29	0.10	0.33		-0.10	0.29	0.10	0.31		
			-	-				-					-					-				High: 13.60
high vs. low	MET-min/week	-0.81	1.06	0.56	<0.001		-0.15	0.35	0.06	0.17		-0.17	0.34	0.01	0.06		-0.16	0.33	0.01	0.06		
Total PA level		N=1907				8623	N=1895				7725	N=1889				6969	N=1889				6973	Low: 13.78
			-					-					-					-				Medium: 13.65
medium vs. low	MET-min/week	-0.19	0.45	0.07	0.16		-0.16	0.37	0.05	0.13		-0.13	0.30	0.04	0.13		-0.13	0.30	0.04	0.13		
			-					-					-					-				High: 13.69
high vs. low	MET-min/week	-0.21	0.47	0.05	0.11		-0.15	0.35	0.06	0.16		-0.10	0.26	0.07	0.27		-0.10	0.26	0.08	0.28		

AIC, Akaike Information Criterion; MET, metabolic equivalent.
Model 1: univariable including a random area effect
Model 2: further adjusted for age, sex, body mass index, education and packyears of smoking
Model 3: further adjusted for mean arterial pressure, heart rate and medication
Model 4: further adjusted for interactions age-sex and sex-mean arterial pressure

Supplementary Figure S1
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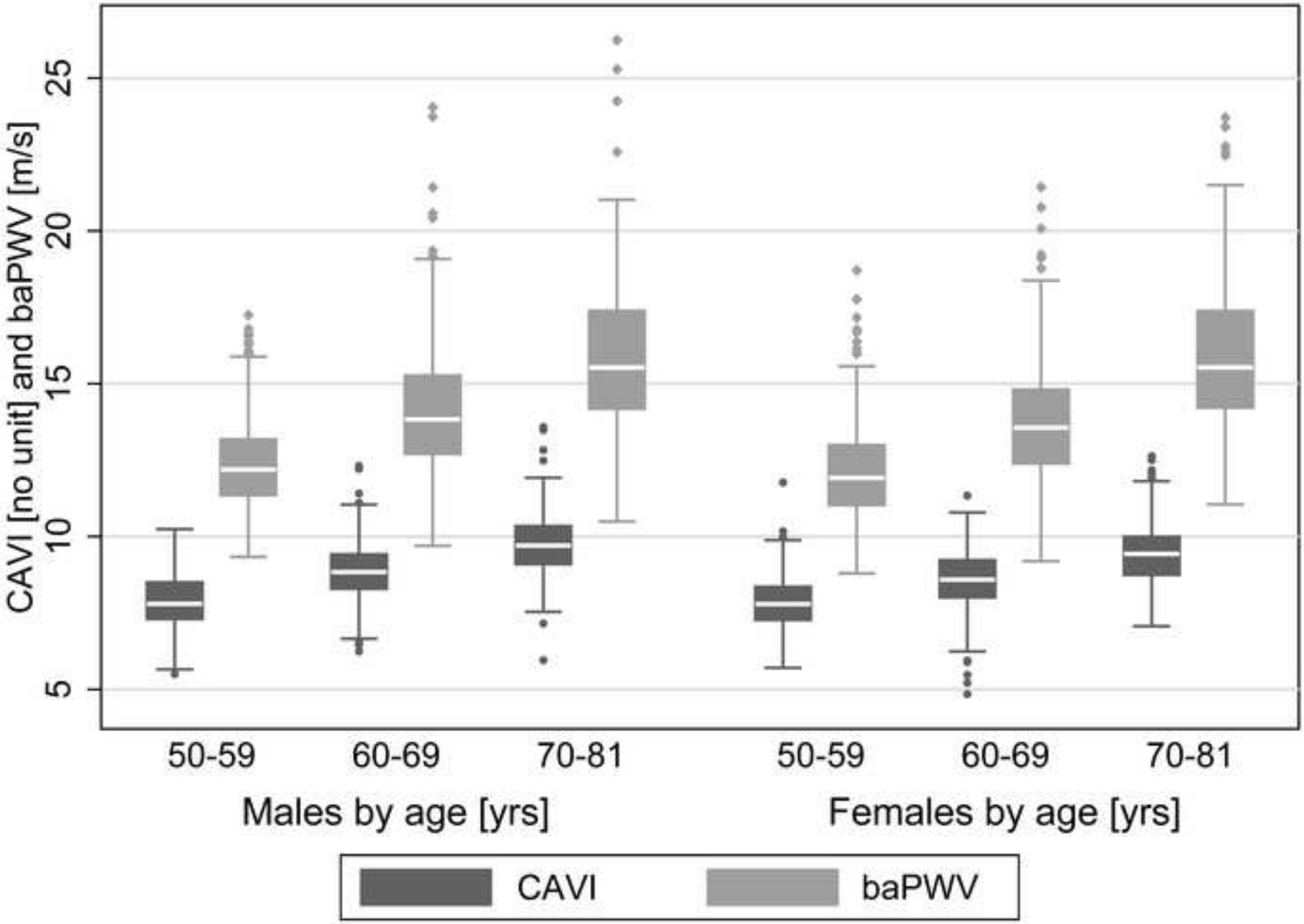

Supplementary Figure S2

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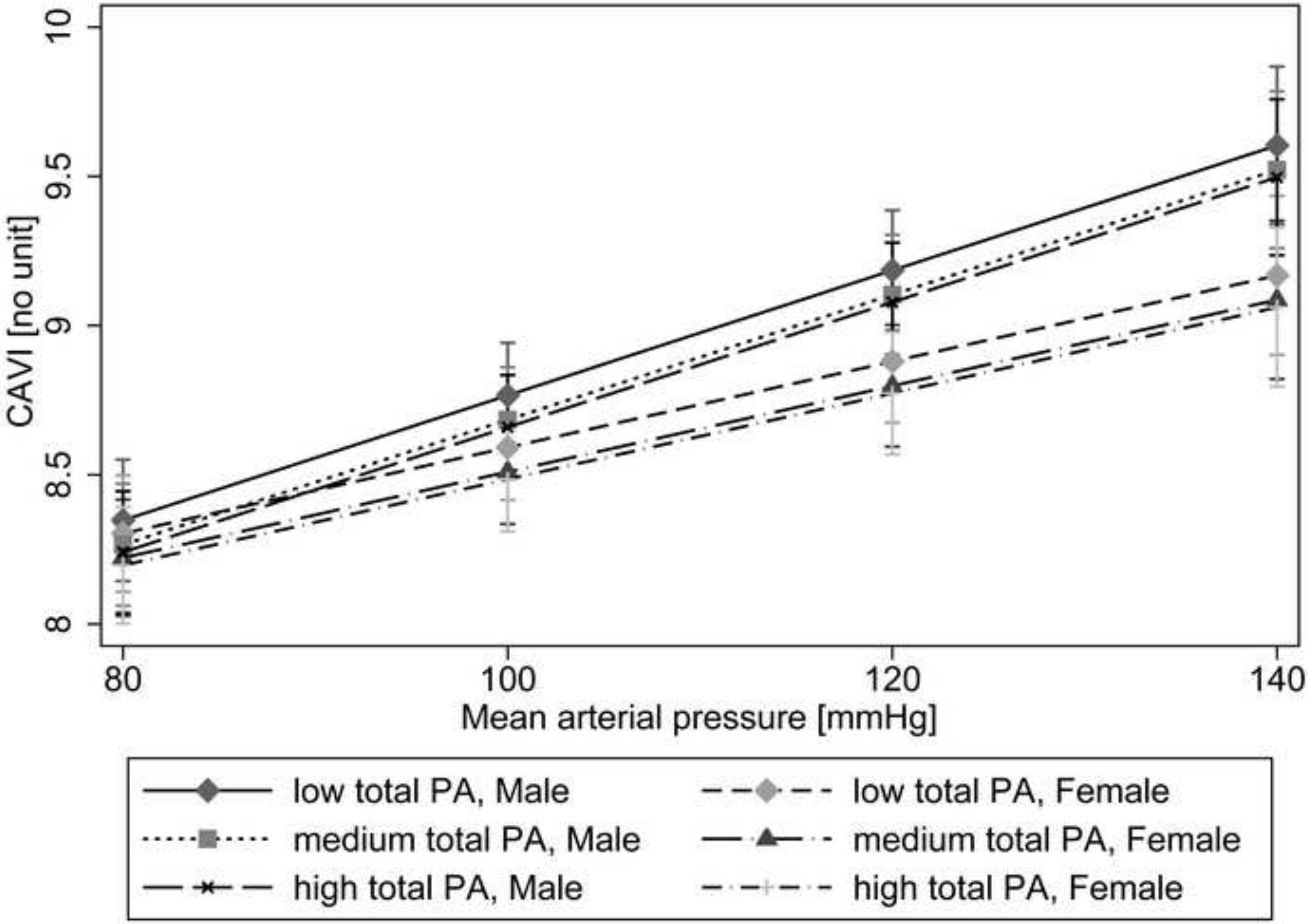

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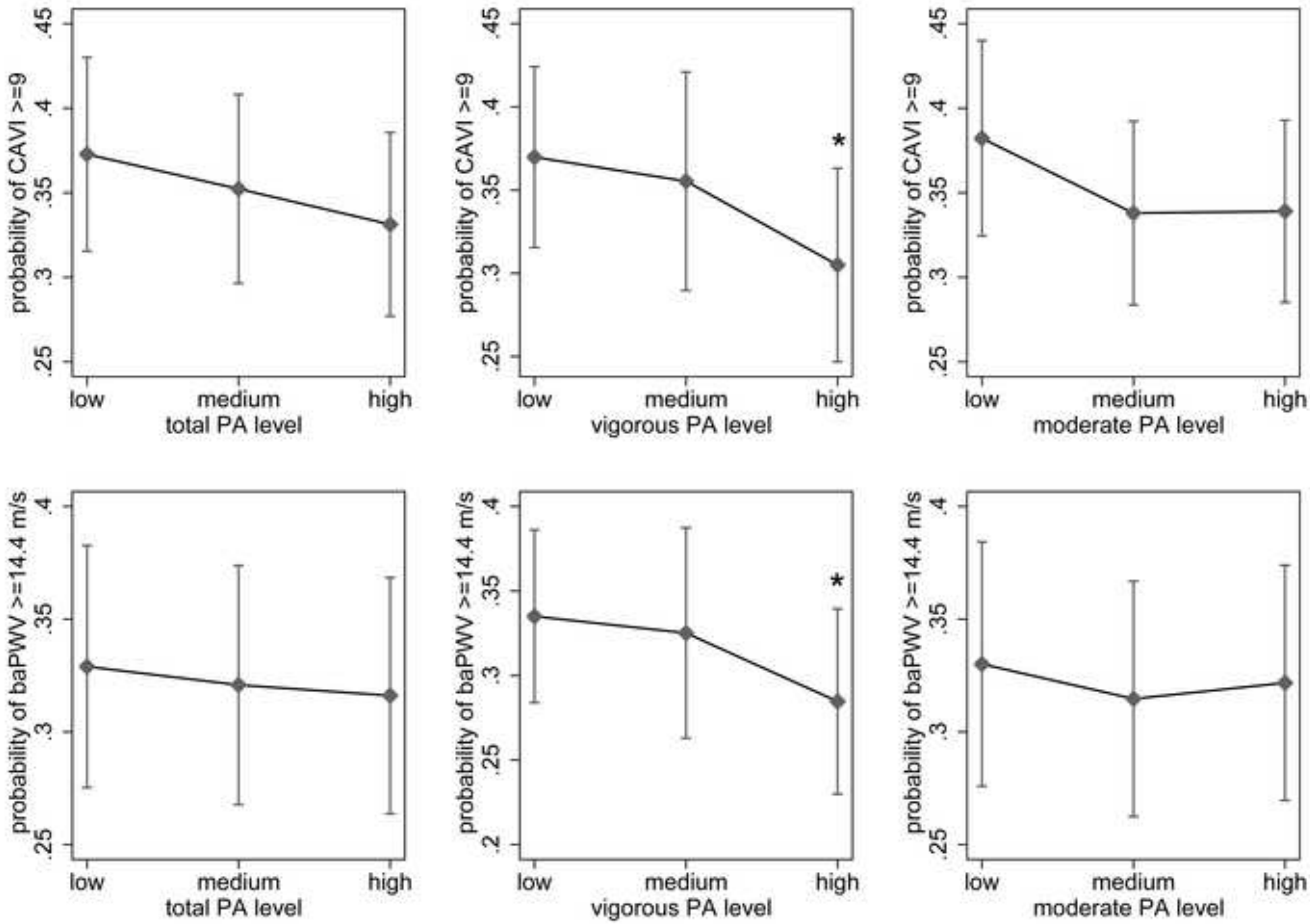

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(a) allergology, (c) cardiology, (cc) clinical chemistry, (e) epidemiology, (exp) exposure, (g) genetic and molecular biology, (m) meteorology, (n) nutrition, (o) occupational health, (p) pneumology, (pa) physical activity, (pd) pediatrics, (s) statistics

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